

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-084

CORRESPONDENCE



Food and Drug Administration
Rockville MD 20857

NDA 21-084

INFORMATION REQUEST LETTER

Department Of The Army
U.S. Army Medical Research and Materiel Command, MCMR-RCQ
Attention: Julie K. Zadinsky, COL, Army Nurse Corps, Deputy Chief of Staff for Regulatory Compliance and Quality
504 Scott Street
Fort Detrick, MD 21702-5012

Dear COL Zadinsky:

Please refer to your August 18, 1999, New Drug Application for NDA 21-084, Topical Skin Protectant.

We are reviewing the Pharmacology/Toxicology, Clinical and Biostatistics sections of your submission and have the following information requests. We need your prompt written response to continue our evaluation of your NDA.

Pharmacology/Toxicology:

Information is needed on anticipated human exposures to chemical warfare agents (CWAs) under field conditions (worse case scenario) and how these exposures relate to the doses used for in vitro and in vivo studies.

Please submit the following information:

1. The concentration (ppm or mg/m^2) of nerve gases to which soldiers may be exposed. How does this concentration relate (multiple) to the concentrations tested in vitro and in vivo?
2. A description of anticipated field exposures to agents such as sulfur mustard and T-2 mycotoxin. How do the concentrations tested in vitro and in vivo compare to potential human exposures based on mg/m^2 ?
3. Any data available on the sensitivity of rabbits to the various CWAs compared to the sensitivity of humans to these agents, i.e., are rabbits more or less sensitive and by what magnitude. Comparison of concentrations and time to onset of clinical signs of toxicity should be submitted for each efficacy end point investigated, e.g., AChE activity, lethality, lesion area and erythema/edema.

Clinical:

1. Concerning the proposed label, please elaborate on the instructions for use/labeling conditions, specifically addressing the following issues:
 - a. Under what environmental conditions can the TSP be applied? Can it be applied outdoors or indoors? If it can be applied outdoors, are there any weather conditions (e.g., wind, rain) that would interfere with TSP application?
 - b. Is the application of TSP compatible with the uniform and all protective gear that would be worn by personnel applying TSP, or just the BDU of the U.S. Army?
 - c. Clarify how personnel will be instructed to rearrange the uniform during and after application (i.e., will they disrobe completely, or roll back/loosen the uniform to gain access to the areas to be protected? Will boots and/or socks be removed to apply the TSP?)
 - d. If there are wounds/abrasions (bandaged or unbandaged) in the areas to be covered with TSP, how does this impact upon the instructions for use and application?
 - e. Explain how the wearing of watches, jewelry, and/or "dogtags" impacts upon the application, efficacy, decontamination, or removal of TSP.
 - f. What instructions will be provided to personnel who inadvertently smear or wipe away the TSP coat while readjusting the BDU or putting on the MOPP gear after application of the TSP?
 - g. Please describe the intended use of the M291 skin decontamination kit.
2. Concerning "Quantitative Fit Factor Evaluation of Topical Skin Protectant (TSP) ICD 2289" (Protocol No. A-6786):
 - a. Please provide the rationale for why subject #19 in this study was withdrawn.
 - b. How were subjects' faces prepared (i.e., were the faces washed) prior to TSP application in the quantitative fit factor test? How was the TSP applied to the face in this test?
3. Concerning "The Protective Efficacy of the Topical Skin Protectant (TSP) Against Methyl Nicotinate Under Sweating Conditions (Protocol No. A-8522)":
 - a. Please provide all collected data in the pilot and main phases in line listing form for the subjects enrolled in this study, including baseline and end-of-treatment LDS data.

- b. Was colorimetry (chromametric), TEWL, SSR data collected in the main phase? If so, please submit these data in the line listings.
- c. Please supply sample case report forms for the main phase of the study.
- d. Please provide an explanation of how the "mean flux" from Laser Doppler Velocimetry Data is calculated.
- e. Please provide an analysis of TSP-Treated versus TSP-Untreated by Type of Challenge.

Biostatistics:

Please submit the following:

- 1. For the clinical study entitled, "An Assessment of the Ability of the TSP to Protect Against Contact Dermatitis to Rhus Antigen (Protocol No. A-6493)":
 - a. The study report on diskette in MS Word 7.0 or better, if available.
 - b. A clear and detailed explanation of the variable names and codes for the SAS data sets Lock_v1.sd2 and Rescore.sd2.
- 2. For the clinical study entitled "The Protective Efficacy of the Topical Skin Protectant (TSP) Against Methyl Nicotinate Under Sweating Conditions (Protocol No. A-8522)":
 - a. The SAS data sets for the Visual erythema, Laser Doppler (LDS), chromametric, Transepidermal Water Loss (TEWL), and Skin surface residue (SSR) data. A detailed explanation of the variable names and codes is needed, if available.
 - b. A detailed description of the statistical analysis comparing TSP-treated versus TSP-untreated relative to LDS, TEWL, SSR, and chromametric data.
 - c. An explanation of the ranking for Table 2E in Volume 41, page 178.
 - d. Prospective definitions of "non-reactors" and "reactors," if any.

**APPEARS THIS WAY
ON ORIGINAL**

If you have any questions, please contact Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

/s/

Mary Jean Kozma-Fornaro
Chief, Project Management Staff
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-084

INFORMATION REQUEST LETTER

Department Of The Army
U.S. Army Medical Research and Materiel Command, MCMR-RCQ
Attention: Julie K. Zadinsky, COL, Army Nurse Corps, Deputy Chief of Staff for Regulatory
Compliance and Quality
504 Scott Street
Fort Detrick, MD 21702-5012

NOV 10 1999

Dear COL Zadinsky:

Please refer to your August 18, 1999, New Drug Application for NDA 21-084, Topical Skin
Protectant.

We are reviewing the Chemistry and Clinical sections of your submission and have the
following information requests. We need your prompt written response to continue our
evaluation of your NDA.

Chemistry, Manufacturing and Controls:

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Clinical:

1. Concerning clinical study "Effects of Topical Skin Protectant (TSP) on Heat Exchange in Humans":
 - a. For all 10 subjects enrolled in this study, please provide line listings of the tolerance time for each subject in the control and the TSP treatment arms of the study.
 - b. Please clarify whether the results in Table 4 (Vol. 2.25, pg. 158) were calculated based on the n=10 or the n=8 subgroup sample. If the results were calculated in the n=8 sample, please perform the corresponding analyses with the n=10 sample, along with a calculation of the p-value from matched pair t-tests.
 - c. The mean Tb at LCM for the control arm appears to be 37.91, not — (as is depicted in the Table 4, Vol. 2.25, pg. 158). Please clarify which of these two statistics is the correct calculation. This should not affect the P-value from the matched pair t-test.
2. Concerning clinical study "An Assessment of the Ability of the Topical Skin Protectant (TSP) to Protect Against Contact Dermatitis to Rhus Antigen", several differences are noted between the instructions in the final protocol (BZ, date of submission 10/19/99) and the TSP Study Technician's Standard Operating Procedure (Vol. 2.24 of NDA submission, page 176-181):
 - a. According to the study protocol, "prior to placement of the test sites, all sites will be wiped with 70% (v/v) isopropyl alcohol and allowed to dry" (page 274 of the October 18, 1999, submission, or page 10 of the protocol). The Standard Operating Procedure does not mention that the test sites should be wiped with isopropyl alcohol and allowed to dry before TSP application. Please clarify whether the test sites were wiped with isopropyl alcohol prior to TSP application.

- b. According to the study protocol, "thirty to sixty minutes after TSP application"(page 274 of BZ submission, or page 10 of the protocol), a 5 microliter aliquot of urushiol solution was applied to the center of coated sites. The Standard Operating Procedure does not mention that there is a 30 to 60 minute time delay between TSP application and urushiol challenge. Please clarify whether there was a time delay between TSP application and urushiol challenge. If there was a time delay, please specify as precisely as possible the extent of the time delay.
- c. The neat concentrations of the 4 stock urushiol solutions used in this study are identified in Vol. 2.26, pg. 098 as 0.570, 0.429, 0.411, 0.623. What are the units for these concentration measurements (i.e., mg/ml, microgram/ml, micromole/ml)?
- d. The clinical protocol does not specify the manner in which urushiol should be applied to the test sites. The Standard Operating Procedure indicates that on the TSP-unprotected site, all three 1.7-microliter aliquots of urushiol solution should be "sequentially placed at the center of the inner 8 mm circle" (Vol. 2.24, pg. 179), as diagramed below. TSP protected sites "should have the 3 aliquots placed in a triangular pattern" (Vol. 2.24, pg. 179) as illustrated below.

TSP Unprotected



TSP Protected



The Standard Operating Procedure states: "note that the technique differs between TSP protected and TSP unprotected sites" (Vol. 2.24, pg. 179).

Please clarify whether the urushiol solution was applied to the TSP Unprotected and TSP Protected sites in the manner outlined in the Standard Operating Procedures. Please provide a rationale for the need for urushiol to be applied in a different manner on the TSP Unprotected and TSP protected sites.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, please contact Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

/S/

Mary Jean Kozma-Fornaro
Chief, Project Management Staff
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 7 PAGES

DRAFT

Labeling



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

21 DEC 1998



Deputy Chief of Staff for
Regulatory Compliance and Quality
Regulatory Affairs Division

SUBJECT: New Drug Application for Topical Skin Protectant
(TSP) (NDA No. 21-084)

Doctor Jonathan K. Wilkin
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



- 8 3 -

Dear Doctor Wilkin:

The U.S. Army Office of The Surgeon General (OTSG) is submitting in triplicate, in accordance with Section 314.50 of Title 21 of the Code of Federal Regulations (21 CFR 314.50), a New Drug Application (NDA) (Form FDA 356h) for Topical Skin Protectant (TSP). The NDA has been assigned No. 21-084. The TSP is a topical barrier cream indicated for protection of the skin from contact with chemical warfare agents (CWA) (blister and nerve agents). It is used in conjunction with appropriate chemical protective clothing and applied prior to exposure to CWA.

Because there is no topical product commercially available or Agency approved that is capable of protecting against chemical warfare agents, and because of the potentially fatal consequences of these agents, we request that this NDA submission be assigned a priority review. It is imperative that every effort be made to accelerate the availability of this product to United States military forces.

This Application is being submitted in accordance with Section 102 of the 1997 Food and Drug Administration Modernization Act Update 21 USC 379g(1) which allows State and Federal Government entities to submit without payment of user fees. The signed User Fee Cover Sheet is at Item 18 of the application.

Reference is made to our series of meetings conducted on April 24, 1995; October 28, 1997; and June 11, 1998 (Post-Phase

II/Pre-NDA) where general agreement was reached on the method of submission. During these meetings, we discussed the extensive non-clinical data supporting the efficacy of TSP as a barrier to exposure to CWA that would be included in this submission. We also obtained concurrence from the Agency for the use of poison ivy resin (Rhus) as a surrogate lipophilic antigen to study the protective effects of TSP against CWA in humans.

During the meeting on June 11, the Agency requested that the results of the efficacy study be re-scored by independent dermatologists in order to avoid any bias that may have occurred. The results of re-scoring the photographs of the poison ivy study are included in the Clinical Data section of this submission.

Additional studies were also suggested by the Agency at the same meeting:

- (1) A sweat study to evaluate the efficacy under extreme conditions.
- (2) An absorption study to confirm that TSP is not absorbed under conditions of multiple use.

[]

We expect that the studies on sweating and absorption will be completed within 30 days, and reports will be submitted to this NDA within 30 days of study completion. Our Institutional Review Board has approved both studies, and subjects are being enrolled. The third study has been planned, but not yet scheduled. We should point out that because of the way the Army trains, the use of TSP will become an integral part of the basic qualifying skills for all Service members. We plan to schedule the test in concert with the training schedule of the units from which subjects will be recruited.

We continue to believe these studies are not necessary for the ultimate approval of TSP; however, rather than entering into discussions on the merits of these studies, we have elected to conduct them. We have chosen to submit this application now, and we expect to submit additional data from the sweat and absorption studies within 60 days. This will expedite the review of what

we believe is a new product with important clinical benefit for the protection of U.S. Service members. We request this application be reviewed on its own merits with the knowledge that these additional studies should be submitted within 60 days. If the Agency finds this unacceptable, we would then request that these studies become Phase 4 requirements.

We also wish to request a waiver from the requirement of Section 126 of the Food and Drug Administration Modernization Act of 1997. Specifically, the requirement to label all products with the symbol "Rx only." This product will not be distributed to Service members under a physician's prescription, but will be distributed to potentially large numbers of individuals at the time when senior leadership believes there is a risk of chemical attack. Including this symbol on the label will, at best, be misleading and could cause unnecessary concern and confusion to medical personnel and other Service members being issued TSP.

Clinical Efficacy Data: In this submission, we present considerable data attesting to the safety and effectiveness of TSP in humans. There are substantial *in vitro* and *in vivo* animal data demonstrating that TSP is an effective barrier preventing or reducing dermal exposure to CWA. Because it is not possible to expose healthy people to lethal doses of CWA, the protective effects of TSP in humans was studied by substituting poison ivy resin, chemically similar to sulfur mustard (HD), as a surrogate CWA against humans. Taken together, the efficacy data is impressive and, when viewed in conjunction with the safety data, makes a compelling argument for approval of TSP.

Chemistry, Manufacturing and Controls (CMC): DoD has contracted with McKesson BioServices of Rockville, Maryland, for the manufacturing development of TSP.

The component drug substances, Fomblin^R Y 25 and Polymist^R F5A, are manufactured by

These are industrial chemicals and to enable them to be used as drug substances has filed Drug Master Files in support of the TSP NDA. In addition, the CMC contains specifications developed by the Army. Since the scale-up lots were produced by a different manufacturer than the laboratory and clinical lots, the Army conducted an independent

validation through a continuing effort at
 Physicochemical and animal efficacy data showed that the McKesson scale-up lots of TSP are equivalent in property and quality to the TSP from the laboratory and clinical lots.

Addresses and telephone numbers for participants in the manufacturing process are provided at Item 19.0, Other. All participants are ready for inspection by the FDA.

This NDA submission is organized into 33 volumes as follows:

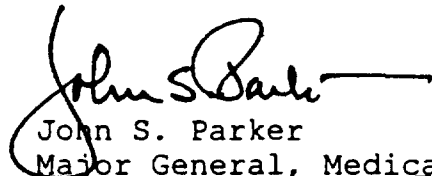
- < Volume 1.1 contains the Application Form (FDA Form 356h), cover letter, Index, and Overall Summary (Items 1 and 2).
- < Volumes 1.2 to 1.11 contain the Chemistry, Manufacturing and Controls section (Item 3) and the Methods Validation Package (Item 3, Volume 1.11).
- < Volume 1.12 contains the Draft Labeling (Item 4).
- < Volumes 1.13 to 1.19 contain the Non-clinical Pharmacology and Toxicology Information (Item 5).
- < Volume 1.20 contains the Human Pharmacokinetics and Bioavailability Information (Item 6).
- < Volumes 1.21 to 1.24 contain the Clinical Data Section (Item 8).
- < Volumes 1.25 to 1.27 contain the Safety Analysis (Item 9).
- < Volumes 1.28 to 1.31 contain the Statistical Information (Item 10).
- < Volume 1.32 contains the Case Report Tabulations (Item 11), and the Case Report Forms (Item 12).
- < Volume 1.33 contains the Patent Information and Certification (Item 13/14), the Establishment Information (Item 15), the Debarment Certification (Item 16), the Field Copy Certification (Item 17), the User Fee Cover Sheet (Item 18), and the Environmental Assessment (Item 19).

We certify that this NDA does not include the services of any persons, debarred clinical investigators, or associated facilities under subsections 306(a) or (b) in the conduct of any of the studies in this submission.

Finally, we look forward to cooperating with you and your staff in the review process in any way possible. Please contact

Dr. Ronald E. Clawson, Project Manager, Pharmaceutical Systems
Project Management Division, U.S. Army Medical Materiel
Development Activity, at 301-619-2051 if you have any questions
or requests regarding this filing. As always, we want to
cooperate fully with the FDA in areas of mutual concerns.

Sincerely,

A handwritten signature in dark ink, appearing to read "John S. Parker", with a horizontal line extending from the end of the signature.

John S. Parker
Major General, Medical Corps
Commander

Enclosure

APPEARS THIS WAY
ON ORIGINAL



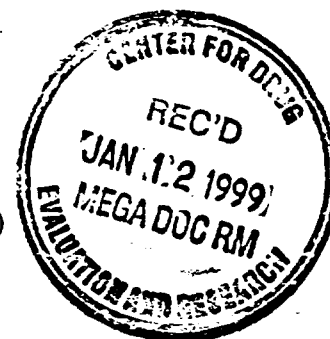
DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY
622 NEIMAN STREET
FORT DETRICK, MARYLAND 21702-5009

ORIGINAL

REPLY TO
ATTENTION OF

WITHDRAWN
WD

January 7, 1999



Pharmaceutical Systems Division

SUBJECT: Withdrawal of New Drug Application (NDA)
No. 21-084 Topical Skin Protectant

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
(HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Doctor Wilkin:

We wish to withdraw NDA No. 21-084 Topical Skin
Protectant, which was submitted December 22, 1998.

In the cover letter of the NDA, we stated that we
expected that two on-going studies, a sweat study (IND
Serial No. 36) and an absorption study (IND
Serial No. 37), would be completed within 30
days and reports would be submitted within 30 days of
study completion. Due to an unforeseen development in
the sweat study, the availability of the study reports
within 60 days of the NDA submission may not be
possible.

During an initial pilot phase of the sweat study,
which began on December 28, 1998, it was observed that
application of methyl nicotinate to five subjects
caused an intense vasodilation on both the TSP
protected and unprotected sites. Although there was
some lengthening of the time to response, time to peak
and spread of the erythematous reactions on the TSP
pretreated sites, the fact that we observed a strong
skin reaction on the TSP pretreated sites was
unexpected. We are currently looking into why the

reactions occurred. In all previous clinical and animal studies, using other challenge agents, we have not seen such a strong reaction on the TSP pretreated sites, other than when the insect repellent, DEET, was used concomitantly.

In the current study, we suspect that the dosages of methyl nicotinate used were excessive (as much as 1000 fold greater than planned). This could account for the rapid onset and intensity of the vasodilation observed. We plan to determine the appropriate dose range and vehicle for administration of methyl nicotinate. These efforts will extend the pilot phase of this study beyond the original plan. It may require an amendment to the current protocol or a new protocol if a challenge agent other than methyl nicotinate is proposed. This new development in the sweat study will delay the submission of the report to the NDA.

We understand that a change in the availability of the study report will impact on your review of the NDA. We believe that the most appropriate course of action would be to withdraw the NDA at this time and resubmit it when the problems have been resolved and the study completed. We estimate that we will resubmit the NDA in mid April. We will keep you informed of the status, particularly if anything would occur which could affect the estimated submission date.

Please contact Dr. Dai Kee Liu, U.S. Army Medical Materiel Development Activity at 301-619-2051, facsimile 301-619-2304, if any questions arise concerning this letter.

Sincerely,

A handwritten signature in black ink, appearing to read 'R. E. Clawson', written over a horizontal line.

Ronald E. Clawson, Ph.D.
Project Manager
Pharmaceutical Systems

Food and Drug Administration
Rockville MD 20857

JAN 26 1999

Department of the Army
US Army Medical Materiel Development Activity
Attention: Ronald E. Clawson, Ph.D.
622 Neiman Street
Fort Detrick, MD 21702-5009

Dear Dr. Clawson :

We acknowledge receipt of your January 7, 1999 correspondence notifying us that you are withdrawing your December 22, 1998 new drug application (NDA) for Topical Skin Protectant that has not been filed.

Therefore, in accordance with 21 CFR 314.65, this application is withdrawn as of the date of our receipt of your notification, January 12, 1999. This withdrawal does not prejudice any future filing of the application. You may request that the information contained in this withdrawn application be considered in conjunction with any future submission. If you resubmit the application, either amended or unamended, the resubmission will be treated as a new original application.

If you have any questions, contact Frank H. Cross, Jr., Project Manager, at (301) 827-2020.

Sincerely,

/S/ 1/25/99

APPEARS THIS WAY
ON ORIGINAL

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
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ORIGINAL



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

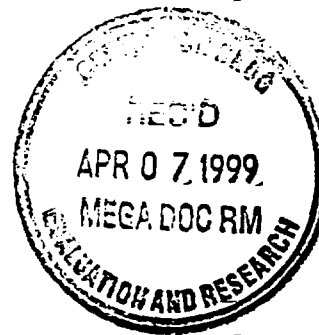
April 1, 1999

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

NEW CORRESP
NC

SUBJECT: Resubmission of the New Drug Application (NDA) 21-084, Topical Skin
Protectant (TSP) (Serial No. 041)

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20850



Dear Doctor Wilkin:

We request your concurrence in the procedure planned for resubmitting the TSP NDA (21-084). Two copies of the TSP NDA (21-084), organized into 33 volumes in accordance with the FDA Guidelines on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications, were submitted to the FDA on December 22, 1998. A field copy of the Chemistry, Manufacturing, and Controls was also provided. On January 7, 1999, the NDA was withdrawn because of a delay in ongoing clinical studies. The results of the ongoing studies were to be added to the NDA by amendment. Although officially withdrawn, the FDA elected to retain the original submission since the NDA would be resubmitted.

On March 23, 1999, Ms. Peggy Hare, Center for Drug Evaluation and Research Central Documents Room, advised us to follow the FDA Guidelines for resubmitting the NDA. She informed us that any additional guidance would have to come from the reviewing division.

We recommend the resubmission be organized by integrating new materials with the materials previously submitted on December 22, 1998, so as to produce a complete submission without unnecessary duplication of documentation. New data, which include newly completed studies (Sweat Study Report, Absorption Study Report, additional stability data, and additional information on method validation), will be integrated into the appropriate volumes of the original NDA. These additions will also affect other volumes impacted by this new information. Some re-formatting will be necessary in order to insert Study Summaries into the appropriate sections of the NDA.

-2-

To avoid confusion, volumes requiring changes will be replaced. Replacement volumes will have a "2." affixed to the volume number on the cover to indicate that it is a resubmission. For example, the original SUMMARY VOLUME, Volume 1.1, will be replaced by Volume 2.1 which will remain as Volume 1 of 33 volumes; Section 6.0, HUMAN PHARMACOKINETICS AND BIOAVAILABILITY, original Volume 1.20 will be replaced by Volume 2.20 which will remain as Volume 20 of 33 volumes. Other reviewing Divisions have accepted this method of identifying replacement volumes. We estimate that approximately one-third of the volumes (11 volumes) will be replaced. The resubmission cover letter will indicate which volumes are being replaced. To assist reviewers who may have made notes in their original review copy, all volumes will include a one-page summary identifying substantive changes and a Table of Contents that identifies added materials.

Fifteen additional copies of Volume 2.1 (the Summary volume) will be provided.

Please contact Dr. Dai Kee Liu, Product Manager, U.S. Army Medical Materiel Development Activity, at 301-619-2051, for specific questions concerning this correspondence. For general regulatory questions, contact Ms. Kathie Mantine at 301-619-2809 (alt. 7550), facsimile 301-619-7803 or Internet address kathie.mantine@amedd.army.mil.

Sincerely,



Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Copies Furnished:

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
Food and Drug Administration, ATTN: CDR Frank Cross, Jr.

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

DUPLICATE

ORIG AMENDMENT

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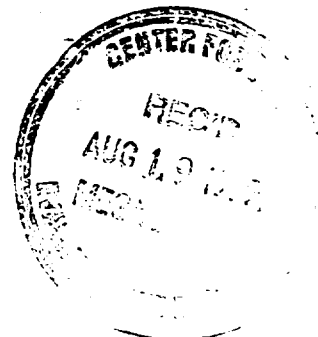
REPLY TO:
ATTENTION OF:

AUG 18 1999

Deputy Chief of Staff for
Regulatory Compliance and Quality

SUBJECT: New Drug Application for Topical Skin Protectant (TSP) (NDA No. 21-084)

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



BEST POSSIBLE COPY

Dear Dr. Wilkin:

The U.S. Army Office of The Surgeon General (OTSG) is resubmitting in triplicate, in accordance with Section 314.50 of Title 21 of the Code of Federal Regulations (21 CFR 314.50), a New Drug Application (NDA) Form FDA 356h for Topical Skin Protectant (TSP). The NDA has been assigned No. 21-084. The TSP is a topical barrier cream indicated for protection of the skin from contact with chemical warfare agents (CWA) (blister and nerve agents). It is used in conjunction with appropriate chemical protective clothing and is applied prior to exposure to CWA.

This NDA is considered an original application, which replaces the NDA documentation previously submitted on December 21, 1998. In accordance with 21 CFR 314.65, the previously submitted application was withdrawn on January 7, 1999, without prejudice to the sponsor, prior to filing in order to permit the completion and integration into the application of two additional clinical studies recommended by the Food and Drug Administration (FDA).

Because there is no topical product commercially available or FDA approved that is capable of protecting against chemical warfare agents, and because of the potentially fatal consequences of these agents, we request that this NDA submission be assigned a priority review. It is imperative that every effort be made to accelerate the availability of this product to United States military forces.

Reference is made to our series of meetings and teleconferences conducted on April 24, 1995; October 28, 1997; June 11, 1998 (Post-Phase II/Pre-NDA); and October 1, 1998 (Teleconference with DDDDP), where general agreement was reached on the method of submission. During these meetings, we discussed the extensive non-clinical data supporting the efficacy of TSP as a barrier to exposure to CWA that would be included in this submission. We

also obtained concurrence from the FDA for the use of poison ivy resin (Rhus) as a surrogate lipophilic antigen to study the protective effects of TSP against CWA, and methyl nicotinate to study the effects of sweating on the protection provided by TSP in humans.

During the meeting on June 11, 1998, the FDA requested that the results of the efficacy study using Rhus antigen be re-scored by independent dermatologists in order to avoid any bias that may have occurred. The results of re-scoring the photographs of the poison ivy study are included in the Clinical Data section of this submission.

The FDA at the same meeting also suggested additional studies:

- (a) A study to evaluate the effectiveness of the TSP under sweating conditions.
 - (b) An absorption study to confirm that TSP is not absorbed under conditions of use.
-

The studies on sweating and absorption have been completed and the reports are included in this NDA. The third study has been planned, but not yet scheduled. We should point out that because of the way the Army trains to protect service members from chemical injuries and contamination, the use of TSP will become an integral part of the basic qualifying skills for all service members. We plan to schedule the user test in concert with the training schedule of those units from which subjects will be recruited.

This Application is being submitted in accordance with Section 102 of the 1997 Food and Drug Administration Modernization Act Update 21 USC 379g(1) which allows State and Federal Government entities to submit without payment of user fees. The signed User Fee Cover Sheet is at Item 18 of the application.

We also wish to request a waiver from the requirement of Section 126 of the Food and Drug Administration Modernization Act of 1997. Specifically, the requirement to label all products with the symbol "Rx only." This product will not be distributed to Service members under a physician's prescription, but will be distributed to potentially large numbers of Service members deployed to war zones or theater of operations where Service members are potentially at risk of CWA attack. Including "Rx only" on the label will be misleading and could cause unnecessary concern and confusion to medical personnel and Service members being issued TSP.

Clinical Efficacy Data: In this submission, we present considerable data attesting to the safety and effectiveness of TSP in humans. Because it is not possible to expose healthy people to lethal doses of CWA, the protective effect of TSP in humans was studied using poison ivy (Rhus) resin, chemically similar to sulfur mustard (HD), as a surrogate CWA against humans.

The use of Rhus as a surrogate for CWA was with the concurrence of the FDA. The sweating study examined in humans the effects of sweating on the protection against exposure to methyl nicotinate, another surrogate for CWA. This also was performed with the concurrence of the FDA. There are also substantial *in vitro* and *in vivo* animal data demonstrating that TSP is an effective barrier preventing or reducing dermal exposure to CWA. Taken together, the efficacy data is impressive and, when viewed in conjunction with the safety data, makes a compelling benefit/risk argument for approval of the TSP.

Chemistry, Manufacturing and Controls (CMC): DoD has contracted with McKesson BioServices of Rockville, Maryland, to develop this CMC section of the NDA.

The component drug substances, Fomblin® Y 25 and Polymist® F5A, are manufactured by _____

_____ These drug substances are industrial chemicals and to enable them to be used as drug substances _____ has filed Drug Master Files for Fomblin® Y 25 and Polymist® F5A in support of the TSP NDA. In addition, the CMC section contains detailed Army developed specifications for these drug substances. McKesson also developed specifications for the TSP drug product. Since the TSP scale-up lots were produced by a different manufacturer than the laboratory and clinical lots, the Army conducted an independent validation through a continuing effort at _____ Physicochemical and animal efficacy data showed that the McKesson scale-up lots of TSP are equivalent in property and quality to the TSP from the laboratory and clinical lots. Addresses and telephone numbers for participants in the manufacturing process are provided at Item 19.0, Other. All participants are ready for inspection by the FDA.

This NDA submission is organized into 41 volumes as follows:

- < Volume 1.1 contains the Application Form (FDA Form 356h), cover letter, Index, and Overall Summary (Items 1 and 2).
- < Volumes 1.2 to 1.11 contains the Chemistry, Manufacturing and Controls section (Item 3) and the Methods Validation Package (Item 3C, Volume 1.11).
- < Volume 1.12 contains the Draft Labeling (Item 4).
- < Volumes 1.13 to 1.19 contains the Non-clinical Pharmacology and Toxicology Information (Item 5).
- < Volumes 1.20 and 1.21 addresses the applicability of Item 7 and contains the Human Pharmacokinetics and Bioavailability Information (Item 6), including the Absorption Study Final Report.
- < Volumes 1.22 to 1.27 contains the Clinical Data Section (Item 8).
- < Volumes 1.28 to 1.30 contains the Safety Analysis (Item 9).
- < Volumes 1.31 to 1.36 contains the Statistical Information (Item 10).
- < Volume 1.37 contains the Case Report Tabulations (Item 11), and the Case Report Forms (Item 12).

- < Volume 1.38 contains the Patent Information and Certification (Item 13/14), the Establishment Information (Item 15), the Debarment Certification (Item 16), the Field Copy Certification (Item 17), the User Fee Cover Sheet (Item 18), and the Environmental Assessment (Item 19, Other).
- < Volumes 1.39 to 1.41 contain the Sweat Study Final Report.

We continually monitor the published literature for new information concerning the safety of TSP for the indicated use. A comprehensive search of the literature was conducted on January 15, 1999 in conjunction with the preparation of the Annual Report for IND ———. An updated search was performed on August 12, 1999. No new published articles concerning the safety of TSP for its intended use were discovered.

The location, in the NDA, of certifications requested by FDA guidance is provided at Enclosure 2 of this cover letter. Available electronic copies of clinical protocols and SAS data sets for clinical studies reports, as requested by CDR Cross, are provided in Item 19 (Other) of the archive copy of the application.

We look forward to cooperating with you and your staff in the review process in any way possible. Please contact Dr. Ronald E. Clawson, Project Manager, Pharmaceutical Systems Project Management Division, U. S. Army Medical Materiel Development Activity, at 301-619-2051 if you have any questions or requests regarding this filing. As always, we want to cooperate fully with the FDA in areas of mutual concerns.

Sincerely,



John S. Parker
Major General, Medical Corps
Commander

Enclosures

Copy Furnished (w/o enclosures):

U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

21-084

APPLICANT INFORMATION

NAME OF APPLICANT

Office of The Surgeon General, Department of the Army

DATE OF SUBMISSION

19 August 1999

PHONE NO. (Include Area Code)

619-2165 or 2602

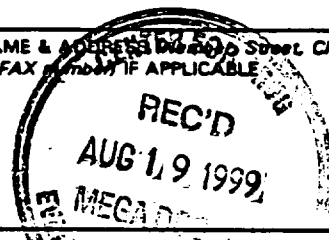
FACSIMILE (FAX) Number (Include Area Code)

301-619-7803

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, U.S. License number if previously issued):

Commander, U.S. Army Medical Research and Materiel Command
IN: MCMR-RCQ-RA
Scott Street
Detrick, MD-21702-5012

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number if applicable)



PRODUCT DESCRIPTION

DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

PUBLISHED NAME (e.g., Proper name, USP/USAN name)

Topical Skin Protectant

PROPRIETARY NAME (trade name) IF ANY

BIOLOGICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSE FORM:

Topical Cream

STRENGTHS:

84 g

ROUTE OF ADMINISTRATION:

Topical

INDICATED INDICATION(S) FOR USE:

Barrier cream against exposure to chemical warfare agents

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50)

☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

ANDA, IDENTIFY THE APPROPRIATE TYPE

☒ 505 (b) (1)

☐ 505 (b) (2)

☐ 507

ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

of Drug

Holder of Approved Application

DATE OF SUBMISSION

(check one)

☒ ORIGINAL APPLICATION

☐ AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

PRE-SUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☐ OTHER

DATE FOR SUBMISSION

USED MARKETING STATUS (check one)

☐ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 41

THIS APPLICATION IS

☒ PAPER

☐ PAPER AND ELECTRONIC

☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Item 19 of the NDA.

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Topical Skin Protectant (ICD 2289): DMF

This application contains the following items: (Check all that apply)

1. Index
2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
3. Summary (21 CFR 314.50 (c))
4. Chemistry section--
 - A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
15. Establishment description (21 CFR Part 600, if applicable)
16. Debarment certification (FD&C Act 306 (k)(1))
17. Field copy certification (21 CFR 314.5 (k) (3))
18. User Fee Cover Sheet (Form FDA 3397)
19. OTHER (Specify) Establishment Information; Environmental Assessment.

DECLARATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of indications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to this application, including, but not limited to the following:

Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.

Biological establishment standards in 21 CFR Part 600.

Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.

In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.

Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.

Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.

Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

All data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

I declare that a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

John S. Parker

TYPED NAME AND TITLE

John S. Parker, MG, MC
Commander

DATE

18 Aug 99

ADDRESS (Street, City, State, and ZIP Code)

Army Medical Research and Materiel Command
Scott Street, Fort Detrick, MD 21702

Telephone Number

(301) 619-7613

The reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

S. Reports Clearance Officer
Work Reduction Project (0910-0338)
Fort H. Humphrey Building, Room 531-H
Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DO NOT RETURN this form to this address.

DA 356h (5/97)

007

ORIGINAL



DEPARTMENT OF THE ARMY

US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

September 2, 1999

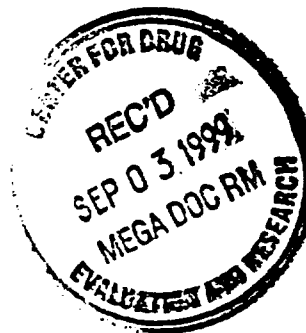
ORIG AMENDMENT

BC

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA) for Topical Skin Protectant (TSP) (NDA No. 21-084);
Amendment #001

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Dr. Wilkin:

Enclosed in triplicate is an amendment to the pending NDA # 21084. This amendment is made in response to a telephonic request from Commander Cross, Project Manager at the Division of Dermatologic and Dental Drug Products. On August 24, 1999, Commander Cross requested that an amendment be submitted to clarify the street address of the manufacturing plant of Fomblin[®] Y25, a drug substance of the TSP, in anticipation of an FDA inspection of the plant in conjunction with review of the NDA. Enclosed are three copies of this amendment: an archival copy (blue) and two review copies (red), one which is marked as the Field Copy of the Chemistry, Manufacturing and Control section of the NDA.

Please contact Ms. Kathie Mantine at 301-649-2809 (alt. 7550), facsimile 301-619-7803, or e-mail kathie.mantine@det.amedd.army.mil for questions concerning this submission. The point of contact at the U.S. Army Medical Materiel Development Activity is Dr. Daikee Liu at 301-619-2051.

Sincerely,

Julie K. Zadinsky

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Enclosures

Copies Furnished (wo/enclosure):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MRMCM-UMP
FED Systems Inc. ATTN: Carl Morin



ORIGINAL



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

September 2, 1999

NEW CORRESP
NC

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA) for Topical Skin Protectant (TSP) (NDA No. 21-084),
Amendment #002

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Dr. Wilkin:

On August 24, 1999, Commander Cross, Project Manager at the Division of Dermatologic and Dental Drug Products, requested additional desk copies of selected volumes of the TSP NDA (NDA No. 21-084) to facilitate its review by the FDA. Enclosed are one copy of each of the following volumes of the NDA. Each is marked "Desk Copy."

<u>Volume Number</u>	<u>Abbreviated Title</u>
1.12	Labeling
1.13	Pharm/Tox
1.16	Pharm/Tox References
1.20	Pharmacology
1.22	Clinical Data
1.23	Clinical References
1.28	Safety

Please contact Ms. Kathie Mantine at 301-619-2809 (alt. 7550), facsimile 301-619-7803, or e-mail kathie.mantine@det.amedd.army.mil for questions concerning this submission. The point of contact at the U.S. Army Medical Materiel Development Activity is Dr. Daikee Liu at 301-619-2051.

Sincerely,

Julie K. Zadinsky

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Enclosures



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

September 24, 1999

REPLY TO
ATTENTION OF:

Office of the Deputy Chief of Staff
For Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA No. 21-084) for Topical Skin Protectant (TSP), Amendment No. 004, Financial Disclosure by Clinical Investigators (21 CFR 54.4)

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857

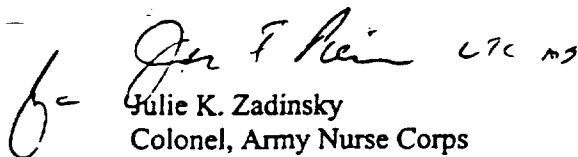


Dear Doctor Wilkin:

Enclosed in triplicate is an amendment to pending NDA No. 21-084, Topical Skin Protectant (TSP). This amendment provides FDA Form 3454 Certification: Financial Interests and Arrangements of Clinical Investigators. This amendment is made in response to the telephonic communication on September 22, 1999, from Commander Frank Cross, Senior Project Manager, Division of Dermatologic and Dental Products, requesting this information per 21 CFR 54.4, Certification and disclosure requirements.

Please contact Ms. Kathie Mantine at 301-619-2809 (alt. 7550), facsimile 301-619-7803, or e-mail kathie.mantine@det.amedd.army.mil for questions concerning this submission. The point of contact at the U. S. Army Medical Materiel Development Activity is Dr. Dai Kee Liu at 301-619-2051.

Sincerely,


Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff
for Regulatory Compliance and Quality

Enclosures

Copies Furnished (wo/enclosures):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
EER Systems Inc., ATTN: Carl Morin



ORIGINAL
DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

September 24, 1999

NEW CORRESP

NC

Office of the Deputy Chief of Staff
For Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA No. 21-084) for Topical Skin Protectant (TSP), Amendment No. 003, Waiver for Pediatric Assessment

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857

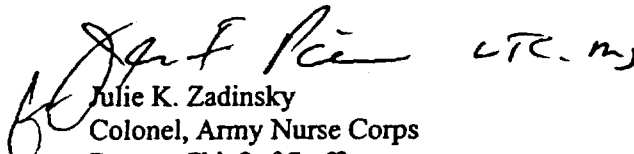


Dear Doctor Wilkin:

Enclosed in triplicate is an amendment to pending NDA No. 21-084, Topical Skin Protectant (TSP). This amendment provides a waiver request pertaining to the 21 CFR 314.55 requirement for pediatric use information. This amendment is made in response to the telephonic request of September 22, 1999 from Commander Frank Cross, Senior Project Manager, Division of Dermatologic and Dental Products. The sponsor did not address this requirement in the NDA submission because TSP is not indicated for pediatric use. Further, the proposed labeling in Item 4.0 of the NDA restricts the use of TSP "For Military Use Only."

Please contact Ms. Kathie Mantine at 301-619-2809 (alt. 7550), facsimile 301-619-7803, or e-mail kathie.mantine@det.amedd.army.mil for questions concerning this submission. The point of contact at the U. S. Army Medical Materiel Development Activity is Dr. Dai Kee Liu at 301-619-2051.

Sincerely,


Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff
for Regulatory Compliance and Quality

Enclosures

Copies Furnished (wo/enclosures):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
EER Systems Inc., ATTN: Carl Morin



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

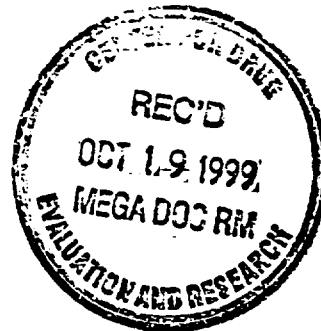
October 19, 1999

REPLY TO
ATTENTION OF:

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA No. 21-084) for Topical Skin Protectant (TSP), Response to
Telephonic Information Request of September 29, 1999

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

Enclosed are two archive and four desk copies of our response to your September 29, 1999 telephonic request on clinical information concerning pending NDA #21-084, Topical Skin Protectant (TSP).

The FDA questions are repeated followed by our responses. Supporting material for our answers, if provided, is attached. As requested, diskettes are provided in two of the desk copies.

Please contact Ms. Kathie Mantine at 301-619-2809 (alt. 7550), facsimile 301-619-7803, or e-mail kathie.mantine@detamedd.army.mil for questions concerning this submission. The point of contact at the U.S. Army Medical Materiel Development Activity is Dr. DaiKee Liu at 301-619-2051.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff
for Regulatory Compliance and Quality

Enclosures

Copies Furnished (w/enclosure):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MRMC-UMP
EER Systems Inc., ATTN: Carl Morin

ORIGINAL

ORIGINAL

DEPARTMENT OF THE ARMY

US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

October 26, 1999

ORIG AMENDMENT



REPLY TO
ATTENTION OF:

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

EM

SUBJECT: New Drug Application (NDA No. 21-084) for Topical Skin Protectant (TSP)

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

Enclosed in duplicate are diskettes containing two clinical protocols to pending NDA No. 21-084, Topical Skin Protectant (TSP), requested by Commander Frank Cross, Senior Project Manager, Division of Dental Drug Products, by telephone on October 22, 1999. The protocols are entitled:

1. "An Assessment of the Ability of the Topical Skin Protectant (TSP) to Protect Against Contact Dermatitis to Rhus Antigen," conducted by Dennis Vidmar, M.D.
2. "The Protective Efficacy of the Topical Skin Protectant (TSP) Against Methyl Nicotinate Under Sweating Conditions," conducted by William Cunningham, M.D.

Please contact Ms. Kathie Mantine at 301-619-2809 (alt. 7550), facsimile 301-619-7803, or e-mail kathie.mantine@det.amedd.army.mil for questions concerning this submission. The point of contact at the U.S. Army Medical Materiel Development Activity is Dr. DaiKee Liu at 301-619-2051.

Sincerely,

Julie K. Zadinsky

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff
for Regulatory Compliance and Quality

Enclosures

Copies Furnished (wo/enclosure):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 S. POTOMAC STREET
FORT DETRICK, MARYLAND 21702-5012

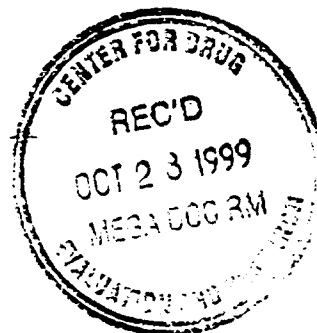
October 27, 1999

REPLY TO
ATTENTION OF:

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA No. 21-084) for Topical Skin Protectant (TSP)

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

Enclosed are 10 hardcopies and 3 diskette copies of an Excel file entitled, "Linelist_Pilot_all methods." The information provided completes our response to Clinical Question 3a from your Information Request Letter of October 12, 1999.

The diskette copy is a single file that contains two spreadsheets. Sheet 1 is a line listing of all data collected during the pilot phase of the clinical study entitled, "The Protective Efficacy of the Topical Skin Protectant (TSP) Against Methyl Nicotinate Under Sweating Conditions," submitted in support of pending NDA No. 21-084, Topical Skin Protectant (TSP). Sheet 2 is a Glossary of Terms for Sheet 1.

Please contact Ms. Kathie Mantine at 301-619-2809 (alt. 7550), facsimile 301-619-7803, or e-mail kathie.mantine@det.amedd.army.mil for questions concerning this submission. The point of contact at the U.S. Army Medical Materiel Development Activity is Dr. DaiKee Liu at 301-619-2051.

Sincerely,

Julie K. Zadinsky

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff
for Regulatory Compliance and Quality

Enclosures

Copies Furnished (wo/enclosure):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MRMC-UMP
EER Systems Inc., ATTN: Carl Morin



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

November 23, 1999

REPLY TO
ATTENTION OF

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA No. 21-084) for Topical Skin Protectant (TSP)

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857

Dear Doctor Wilkin:

Enclosed are four official and four desk copies of the information requested in your Information Request Letter of November 10, 1999 concerning pending NDA 21-084, Topical Skin Protectant (TSP). Enclosure 1 contains responses to questions on Chemistry, Manufacturing, and Controls. Enclosure 2 contains responses to clinical questions. In each response the FDA question is repeated in bold type followed by our response.

Please contact Ms. Kathie Mantine at 301-619-2809 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amcdd.army.mil for questions concerning this submission. The point of contact at the U.S. Army Medical Materiel Development Activity is Dr. DaiKee Liu at 301-619-2051.

Sincerely,

Julie K. Zadinsky

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff
for Regulatory Compliance and Quality

Enclosures

Copies Furnished (wo/enclosure):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MRMC-UMP
EER Systems Inc., ATTN: Carl Morin

December 3, 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NEW CORRECTION
NC

William C. Timmer, Ph.D.
U.S. Food and Drug Administration, CDER
Division of Dermatologic and Dental Drug Products, HFD-540
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, MD 20857

RE: NDA # 21-084 Fomblin Y25 TSP

On November 15 -17, 1999, Mr. Jorge L. Gonzalez, Investigator for the FDA, conducted an inspection of the _____ facility in reference to the US Army NDA 21-084 for Topical Skin Protectant. The focus of the inspection was the manufacturing process for Fomblin Y25 TSP. The following observation was identified on the Form FDA 483 issued at the conclusion of the inspection on November 17, 1999.

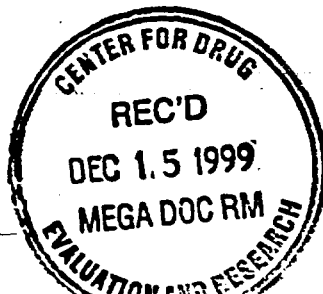
Firm has no formal stability study program which would include the stability testing program and sample storage conditions. (Product: Fomblin Y25 TSP)

During the inspection, on November 16, 1999, _____ provided the investigator a signed letter by _____ that committed to developing and implementing a stability protocol for Fomblin Y25 TSP for inclusion in Drug Master File No. _____. The stability protocol and Statement of Commitment will be submitted to the DMF by February 2000 as a part of the complete response to the Dr. Wilson H. DeCamp, Ph.D. letter dated September 24, 1999.

_____ trusts that this action will be acceptable. If you have any questions or require any additional information, please contact me at _____

Director - Regulatory Affairs

cc: Jorge Gonzalez, FDA



ORIGINAL

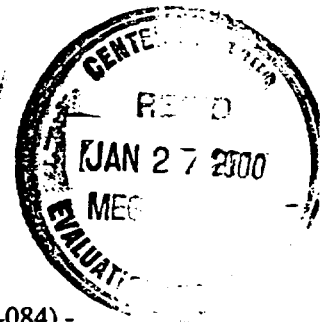


DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

January 26, 2000

REPLY TO
ATTENTION OF:

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality



SUBJECT: New Drug Application (NDA) for Topical Skin Protectant (TSP) (NDA No. 21-084) -
Response to FDA Request for Information

NDA 21-084 AMENDMENT

be

Jonathan K. Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857

Dear Doctor Wilkin:

Enclosed are four copies of our response to the January 5, 2000 telephonic request from CDR Frank Cross, Project Manager at the Division of Dermatologic and Dental Drug Products, regarding Stability Concerns in the pending NDA 21-084, Topical Skin Protectant (enclosure 1). CDR Cross requested that we respond to two items: 1) submitting additional stability data to support 18 months expiration dating, and 2) submitting data on the new proposed packaging and committing the three-point stability program.

Our specific responses to the two items are the following:

1. The additional stability data are at enclosure 2.

a. Tables 1-4 contain data on Long Term Stability testing at 30 °C/60 percent relative Humidity (RH) of batches TSP004, TSP005, and TSP006 packaged in the original pouch materials (NDA Volume 1.10, page 27). Specifically, the 12- and 18-month stability data are included. The data showed that the TSP was stable up to 18 months at 30 °C/60 percent RH.

b. Tables 5-15 contain Accelerated Stability testing at various temperatures (-40, 30, 45, and 70 °C) of batches TSP004, TSP005, and TSP006 packaged in new pouch materials (NDA Volume 1.2, page 281; NDA Volume 1.10, pages 378-382). The data showed that the TSP was stable up to 6 or 8 months at various temperatures (-40, 30, 45, and 70 °C).

2. Information on new proposed packaging and committing to three-point stability program:

a. Information, including material physical properties and seal strength on the new packaging materials, are in the NDA Volume 1.10, pages 378-390.

b. Agency's three-point stability program (enclosure 1).

DUPLICATE

Agency request:

- (1) "The first three batches manufactured post-approval will be placed on stability."
- (2) "At least one batch per year (preferentially one batch per every ten manufactured) will be placed on stability."
- (3) "The Applicant will advise the Agency immediately and will issue a recall of the drug if necessary, if the stabilities reveal a failure."

Response:

- (1) The U.S. Army will commit that the first three batches manufactured post-approval will be placed on stability under current contract.
- (2) To place at least one batch per year (preferably one batch per every ten manufactured) on stability will require the Army and DoD to dedicate resources and funds over the long term (e.g. 10 years). Although this Command cannot commit funds beyond current Congressional appropriation and contractual limitations, the Command assures the Agency that it will expend every resource to assimilate this requirement into the Army or DoD's medical acquisition and logistics organizations upon NDA approval.
- (3) The U.S. Army will advise the Agency immediately and will issue a recall of the drug if stability reveals a failure. As indicated in item (2) above, this Command will do its best to assimilate this requirement to DoD's medical acquisition and logistic organizations.

Please contact Ms. Kathie Mantine at 301-619-2809 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions. The point of contact at the U.S. Army Medical Materiel Development Activity for technical questions is Dr. DaiKee Liu at 301-619-2051 or facsimile 301-619-2304.

Sincerely,



Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Copies Furnished:

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
McKesson BioServices, ATTN: Dr. Robert Rice



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

February 1, 2000

REPLY TO
ATTENTION OF:

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA) for Topical Skin Protectant (TSP) (NDA No. 21-084) -
Response to FDA Waiver Request

Jonathan K. Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

We hereby request a waiver for lot-to-lot Microbial Limit Test for TSP. This waiver request is based on a telephonic request from CDR Frank Cross, Project Manager at the Division of Dermatologic and Dental Drug Products, on January 31, 2000 because of the inert nature of the TSP.

The TSP contained two non-aqueous, chemically inert drug substances: Polymist F5A, a polytetrafluoroethylene, and Fomblin Y25, a perfluoroalkylpolyether. These two drug substances do not provide nutrient support for microbial growth. We have conducted Microbial Limit Test on the two drug substances (three lots each) and TSP (six lots) all with negative results. We agree with the Agency's view that it is unlikely that TSP will support microbial proliferation and Microbial Limit Test for TSP is unnecessary.

Please contact Ms. Kathie Mantine at 301-619-2809 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions. The point of contact at the U.S. Army Medical Materiel Development Activity for technical questions is Dr. DaiKee Liu at 301-619-2051 or facsimile 301-619-2304.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Copies Furnished:

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
McKesson BioServices, ATTN: Dr. Robert Rice

DUPLICATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

NDA 21-175

APPLICANT INFORMATION

NAME OF APPLICANT

Department of the Army, Office of The Surgeon General

DATE OF SUBMISSION

1 Feb 00

TELEPHONE NO. (Include Area Code)

301-619-2165 or 2602

FACSIMILE (FAX) Number (Include Area Code)

301-619-7803

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

Commander, U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-RA
504 Scott Street
Fort Detrick, MD 21702-5012

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Topical Skin Protectant

PROPRIETARY NAME (trade name) IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSAGE FORM:

Soft Pack

STRENGTHS:

84g

ROUTE OF ADMINISTRATION:

Topical

(PROPOSED) INDICATION(S) FOR USE:

Barrier cream against exposure to chemical warfare agents.

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

☐ NEW DRUG APPLICATION (21 CFR 314.50)

☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

☒ 505 (b) (1)

☐ 505 (b) (2)

☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one)

☐ ORIGINAL APPLICATION

☐ AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

☐ PRESUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☒ OTHER

REASON FOR SUBMISSION

Response to FDA request for information.

PROPOSED MARKETING STATUS (check one)

☐ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS

☐ PAPER

☐ PAPER AND ELECTRONIC

☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND — Topical Skin Protectant (ICD 2289); DMF



U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

February 8, 2000

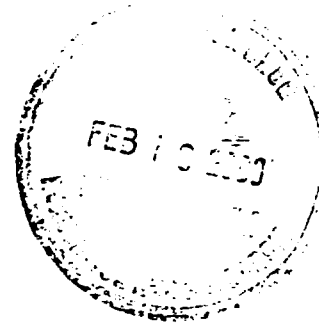
NC

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

ENCLOSURE

SUBJECT: New Drug Application (NDA) for Topical Skin Protectant (TSP) (NDA No. 21-084)
- Response to FDA Request for a New Product Name

Jonathan K. Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

We hereby submit a name change for the New Drug Application "Topical Skin Protectant (TSP)" to "Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA)". This submission is based on your concern, expressed in a telephonic conversation on January 28, 2000, that naming the product "Topical Skin Protectant (TSP)" is not appropriate because of ambiguity in its intended use.

Please contact Ms. Kathie Mantine at 301-619-2089 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions concerning this submission. The U.S. Army Medical Materiel Development Activity point of contact for technical questions is Dr. DaiKee Liu at 301-619-2051 or facsimile 301-619-2304.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Copies Furnished:

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
U.S. Army Medical Materiel Agency, ATTN: MCMR-MMT
McKesson BioServices, ATTN: Dr. Robert Rice

ORIGINAL



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

February 11, 2000



Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA) for Topical Skin Protectant (TSP) (NDA No. 21-084)
- Response to FDA Request for Information

Jonathan K. Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857

Dear Doctor Wilkin:

Enclosed is the information on packaging materials for the New Drug Application (NDA) for Topical Skin Protectant (TSP) (NDA No. 21-084) requested by CDR Frank Cross on February 10, 2000. This information was also sent to CDR Cross by facsimile on February 10, 2000.

Please contact Ms. Kathie Mantine at 301-619-2089 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions concerning this submission. The U.S. Army Medical Materiel Development Activity point of contact for technical questions is Dr. DaiKee Liu at 301-619-2051 or facsimile 301-619-2304.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Copies Furnished:

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
U.S. Army Medical Materiel Agency, ATTN: MCMR-MMT
McKesson BioServices, ATTN: Dr. Robert Rice



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

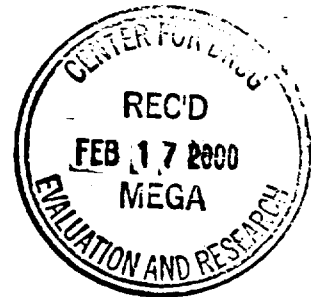
February 16, 2000

RESP
NC

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA) for SERPACWA (NDA No. 21-084) - Response to
FDA Waiver Request

Jonathan K. Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

Enclosed is the information on packaging materials for the New Drug Application (NDA) for SERPACWA (NDA No. 21-084) requested by CDR Frank Cross during a telephone call on February 15, 2000. This is the same information that was sent to CDR Cross by facsimile on February 16, 2000.

Please contact Ms. Kathie Mantine at 301-619-2809 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions. The point of contact at the U.S. Army Medical Materiel Development Activity for technical questions is Dr. DaiKee Liu at 301-619-2051 or facsimile 301-619-2304.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Enclosure

Copies Furnished (wo/enclosure):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
U.S. Army Medical Materiel Agency, ATTN: MCMR-MMT
McKesson BioServices, ATTN: Dr. Robert Rice



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

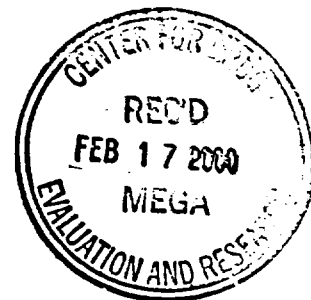
February 16, 2000

NC

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application (NDA) for SERPACWA (NDA No. 21-084) - Response to FDA
Proposed Draft Labeling

Jonathan K. Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

Enclosed are four copies of our proposed changes to the SERPACWA draft labeling. We received the draft labeling from CDR Frank Cross on February 11, 2000. An electronic version of our proposed changes using Microsoft Word editing functions is provided with this transmittal for your convenience.

Please contact Ms. Kathie Mantine at 301-619-2089 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions concerning this submission. The U.S. Army Medical Materiel Development Activity point of contact for technical questions is Dr. DaiKee Liu at 301-619-2051 or facsimile 301-619-2304.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Enclosures

Copies Furnished (wo/enclosures):

U.S. Army Medical Research and Materiel Command, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP
U.S. Army Medical Materiel Agency, ATTN: MCMR-MMT

DUPLICATE



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

February 16, 2000

REPLY TO
ATTENTION OF:

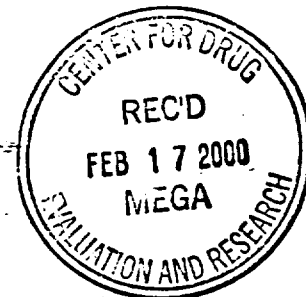
Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

NEW CORRESP

NC

SUBJECT: New Drug Application (NDA) for SERPACWA (NDA No. 21-084) - Response to FDA
Draft Phase 4 Commitments

Jonathan K. Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857



Dear Doctor Wilkin:

Enclosed are our responses to the proposed Phase 4 commitments which we received from CDR Frank Cross on February 11, 2000 (enclosure 1). The Agency's proposed Phase 4 studies are found in bold followed immediately by our specific responses. Also included is a report from the study entitled, "The Effect of a Candidate Topical Skin Protectant" ————— on the Efficacy of the M291 Skin Decontamination Kit Against TGD and HD in the Rabbit" (enclosure 2).

The conduct of the Phase 4 studies recommended by the Agency will require fiscal year 2000 and fiscal year 2001 funds. We are not authorized to commit fiscal year 2001 funds that are not yet appropriated and approved by Congress. However, we will plan to conduct the studies that are agreed upon between the Agency and the U.S. Army Medical Research and Materiel Command. Completion of these studies in one year is unrealistic due to fiscal constraints of the current budget cycle. Therefore, we will plan to complete these studies in two years, subject to the availability of funds.

Please contact Ms. Kathie Mantine at 301-619-2089 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions concerning this submission. The U.S. Army Medical Materiel Development Activity point of contact for technical questions is Dr. DaiKee Liu at 301-619-2051 or facsimile 301-619-2304.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

DUPLICATE



DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY
622 NEIMAN STREET
FORT DETRICK, MARYLAND 21702-5009

REPLY TO
ATTENTION OF.

Pharmaceutical Systems Division

February 17, 2000

SUBJECT: New Drug Application (NDA) for SERPACWA, formerly
Topical Skin Protectant (TSP), NDA No. 21-084 -
response to Phase 4 commitment and draft labeling

Jonathan K. Wilkin, M.D.

Director, Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, Maryland 20857

Dear Dr. Wilkin:

We have reviewed the latest versions of the Phase 4
Commitments and labeling that CDR Frank Cross, Senior Project
Manager at the Division of Dermatologic and Dental Products sent
to us by facsimile transmittal on February 17, 2000. We agree
with the proposed Phase 4 commitments that you outlined. We
will submit relevant protocols to the Agency for review and
comment before initiating the studies. We also agree with
revisions you made in this version of labeling.

The point of contact at the U.S. Army Medical Materiel
Development Activity is Dr. Dai Kee Liu at 301-619-2051,
facsimile 301-619-2304.

Sincerely,

Ronald E. Clawson, Ph.D.
Project Manager
Pharmaceutical Systems

BEST POSSIBLE COPY

Teleconference Date: January 5, 2000

Time: 1015

Location: N229

NDA 21-084; Topical Skin Protectant

Applicant: U.S. Army Medical Materiel Development Activity (USAMMDA),
Ft. Detrick, MD

Purpose of Meeting: Discussion of Stability Concerns

Meeting Chair: Frank H. Cross, Jr., M.A., CDR

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830

William Timmer, Ph.D., Chemist, DNDCIII, HFD-830

Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Dai Kee Liu, Ph.D., Product Manager, PSD

Agency:

1. A 12 month expiration date (or shelf life) for drug stored below 30° C is the maximum expiration date that is supported for this drug provided the NDA is approved. Additional data to support a longer expiration date should be submitted as a Prior Approval Supplement to the NDA
2. The drug product manufacturer is limited to batches of — size, provided that the NDA is approved. Any change in batch size must be submitted as a Prior Approval Supplement to the NDA.
3. Delamination of the drug product package on storage at elevated temperatures was discussed with the Sponsor.

Applicant:

The Applicant may be submitting additional stability data to support an 18 month expiration dating. The Applicant has been investigating new packaging for this drug product and will submit data collected on the new packaging in the near future.

NDA 21-084, Topical Skin Protectant
Memorandum of Teleconference
Page 2

Agency:

1. The Agency will review the Applicant's additional stability data which will be submitted in the next few days to ascertain if an 18 month expiration date can be supported.
2. The Applicant was advised to submit data on the new proposed packaging for this drug as a Prior Approval Supplement to the NDA.
3. The Agency requested that the Applicant formally commit to the following 3 point stability program:
 - a. The first three batches manufactured post-approval will be placed on stability.
 - b. At least one batch per year (preferably one batch per every ten manufactured) will be placed on stability.
 - c. The Applicant will advise the Agency immediately and will issue a recall of the drug if necessary, if the stability studies reveal a failure.

Applicant:

The Applicant will make the requested submissions and thanked the Agency for its feedback and guidance.

None.

Signature, minutes preparer

/S/

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 15, 2000

Number of Pages (including cover
sheet) - 13

TO: Dai Kee Liu, Ph.D., Product Manager, Pharmaceutical Systems
COMPANY: U.S. Army Medical Materiel Development Activity, Fort Detrick, MD
FAX #: 301-619-2304

MESSAGE: Please indicate your acceptance of the attached proposed labeling for this NDA.
The additional items are in bold.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 12 pages

Draft

Labeling

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 17, 2000

Number of Pages (including cover sheet) - 2

TO: Dai Kee Liu, Ph.D., Product Manager, Pharmaceutical Systems
COMPANY: U.S. Army Medical Materiel Development Activity, Fort Detrick, MD
FAX #: 301-619-2304

MESSAGE: Please indicate your acceptance of the below-listed Phase 4 Commitments:

These commitments, to be completed within two years of approval of the NDA, are listed below:

PHARMACOLOGY/TOXICOLOGY:

Due to the possible adverse effects associated with smoking products contaminated with TSP, it is recommended that the Applicant perform a nonclinical study to evaluate long-term effects of acute exposure to polytetrafluoroethylene fumes.

CLINICAL:

1. Conduct a study to characterize the compatibility of SERPACWA with the Battle Dress Uniform/overgarment and overboots.
2. Conduct a study to determine the extent to which SERPACWA is transferred to smoking products when smoking products are handled by subjects whose hands have been coated with SERPACWA during the process of applying SERPACWA to body surfaces, and who have not washed their hands prior to handling of smoking products. If SERPACWA does transfer to smoking products when the smoking products are handled by subjects who have not washed their hands prior to handling of smoking products, the studies should also address whether washing of hands prior to handling of smoking products reduces the transfer of SERPACWA to smoking products.

3. Conduct an actual use study to determine whether subjects can apply on themselves a thin coat of Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA) that reduces or prevents the penetration of a dermal permeant to include:
 - a. Demonstration that the cutaneous barrier property is immediate upon Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA) application, or the time interval needed to establish the barrier,
 - b. Characterization of how long the barrier effect remains on the skin,
 - c. Characterization of the consequences of not cleaning the skin with isopropyl alcohol prior to Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA) application on the barrier properties of Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA), and
 - d. Characterization of the potential interactions between the M291 Skin Decontamination Kit and Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA).-

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. The Phase 4 final study reports should be submitted to the Agency within two years of NDA approval. Please submit the relevant protocols to the Agency for review and comment before initializing the studies.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 17, 2000

Number of Pages (including cover
sheet) - 14

TO: Dai Kee Liu, Ph.D., Product Manager, Pharmaceutical Systems
COMPANY: U.S. Army Medical Materiel Development Activity, Fort Detrick, MD
FAX #: 301-619-2304

MESSAGE: Please indicate your acceptance of the attached labeling for this NDA.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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